Benzene

Chemical Summary Form

U.S. EPA, Toxicity and Exposure Assessments for Children's Health

SPECIAL CONCERNS FOR CHILDREN FROM BENZENE

HUMAN EXPOSURE/EFFECTS

- Studies on prenatal benzene exposure have shown varying effects in both the mother and fetus. One study showed no increase in miscarriage for women exposed to benzene (1), while two other studies showed effects including increased rate of miscarriage and decreased birth weight (2, 3). Another study suggested a genetic predisposition to adverse reproductive effects from benzene exposure (4).

- Parental exposure to benzene has been correlated with hematologic cancer in children. Two studies have shown an increased risk of childhood leukemia associated with paternal exposure to benzene (5, 6), while another showed no such association (7). A case control interview study showed that acute nonlymphocytic leukemia was linked to maternal occupational exposure to benzene during pregnancy (8).

- Benzene has been detected in fetal cord blood at levels equal to or greater than those levels found in maternal blood (9).

- A number of studies have examined the relationship between benzene exposure from traffic pollution and childhood cancer rates. A study of over 5,000 Danish children showed that the risk of lymphoma significantly increased when benzene exposures (from pollution due to traffic) during pregnancy doubled (10). Another case control study suggested an association between proximal high traffic density streets and childhood cancer, including leukemia (11). However, data from a recent study (2002) showed little or no evidence for association between childhood cancer rates and living in high traffic neighborhoods (12).

- Increased levels of the benzene metabolite trans, trans-muconic acid (biomarker of benzene exposure) in urine of children 11-14 years of age correlated with proximity to high traffic areas and not to cigarette smoke exposure (13). However, the correlation of this non-specific biomarker with benzene exposure remains equivocal (14).

- Benzene exposure via inhalation has been associated with hematologic changes in children. One study found changes in blood cell counts as compared to controls, in Korean children who lived near a petrochemical plant, where air benzene levels were 6-15 times higher for the exposed group than the control group (15).

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- Benzene exposure has also been associated with respiratory difficulties in children, including increased occurrence of wheezing in children under 2 years of age (16) and increased incidence of obstructive bronchitis (17) and bronchopneumonia (18).

EXPERIMENTAL ANIMAL EXPOSURE/EFFECTS

- Benzene was found to be a transplacental genotoxicant in mice in one study, causing a significant increase in micronuclei and sister chromatid exchange in both maternal bone marrow and fetal liver cells at higher doses (19). A second study replicated these results, showing a significant increase in sister chromatid exchange in both maternal and fetal cells at the highest dose (20). However, another study did not find genotoxic activity of benzene or its metabolites in pregnant dams' cells while micronuclei in fetal liver cells were induced (21).

- Male mice, but not female mice, were found to have reduced numbers of erythrocyte precursor cells after benzene exposure. One review of animal studies on benzene exposure corroborated this result, finding marked sex differences in susceptibility during germ cell formation (22). Results from another study suggested that the male erythron (the circulating erythrocytes in the blood, their precursors, and all the elements of the body concerned in their production) is more susceptible than the female erythron to benzene exposure for *in utero* and adult exposures (23).

- Several studies have shown that benzene exposure may be hematotoxic. In one study, mice exposed *in utero* to concentrations of benzene at the current occupational exposure limit were found to have alterations of the hematopoietic system which persisted into adulthood (24). Another similar study, in which mice were exposed *in utero* to benzene, found a reduced number of erythrocyte precursor cells at two days of age, and this effect persisted to adulthood (25).

- Prenatal exposure to benzene in some animal studies resulted in reduced birth weights, delayed bone formation, neurological abnormalities, and immunological abnormalities in pups at doses that did not cause maternal toxicity (26-28). Other animal studies showed no such adverse developmental effects (29-31). Rat studies have shown embryotoxic (32, 33) and fetotoxic (34) effects at levels that caused toxicity to the mother. In a similar study in mice and rabbits, maternal benzene inhalation resulted in embryonic toxicity with little evidence of maternal toxicity (35).

- In one study, benzene was detected in fetal cord blood with levels equal to or greater than those found in maternal blood (9). However, a study in mice, which evaluated placental transfer of benzene after inhalation, showed no retention of benzene metabolites in the feto-placental unit (36).

- Increased incidence of multiple cancers was observed following early life inhalation exposure in mice and rats (37).

CONSIDERATIONS FOR DECISION-MAKING

- A large-scale, multi-city personal air sampling study of many chemicals including benzene, and in which children ages 7 and older were included, was performed by the U.S. EPA Total Exposure Assessment Methodology Study (TEAM) (38, 39). Environmental tobacco smoke contributed to benzene exposure, with indoor benzene levels 30-50% higher in smoking homes than nonsmoking homes (39).
- Benzene was included in the chemicals assessed in the National Human Exposure Assessment Survey (NHEXAS) which analyzed samples of indoor and outdoor air and drinking water for benzene. Indoor benzene air concentrations exceeded outdoor air concentrations. Most drinking water samples had benzene concentrations below the analytical limit of detection (40, 41).
- Children's exposure to benzene via vehicle exhaust is not well characterized but should be considered when doing an exposure assessment because multiple studies have suggested vehicle exhaust may contribute to residential benzene exposure (42).
- Benzene in contaminated groundwater can volatilize and contaminate indoor air (43, 44).
- An alternate water supply, e.g. bottled water, should be considered where benzene-contaminated ground water may be impacting drinking water.
- Consult "Child-Specific Exposure Factors Handbook," EPA-600-00-002B, for factors to assess children's drinking water consumption and inhalation rates.
- Childhood is a sequence of lifestages rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.

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EXPOSURE[1]

Exposure Media	Level of Concern[2]	Basis
Indoor Air	Higher	Benzene is a common indoor air pollutant. Sources include cigarette smoke; exhaust from motor vehicles; smoke from wood burning fires; and some household products which contain petroleum-based chemicals such as glues, paints, furniture wax, and lubricants. In homes/dwellings located above contaminated groundwater, benzene vapor is capable of migrating through soil and foundations to enter basements or living spaces and contribute to indoor air concentrations. Benzene could also volatilize to indoor air from contaminated groundwater due to indoor water uses (e.g., showering, dishwashing, laundry).
Ambient Air	Medium	Benzene is a common ambient air pollutant. Outdoor air contamination sources include exhaust from motor vehicles, and emissions from industrial processes and motor vehicle service stations.
Groundwater	Medium	Groundwater contamination can occur from leaking underground storage tanks and from hazardous waste sites where benzene is often present as a component of gasoline and petroleum products.
Soil	Lower	Benzene is a volatile compound that does not undergo significant partitioning or accumulation in soils. Low concentrations of benzene in surface soils may be detectable at locations where accidental spills of gasoline or petroleum have occurred.
Diet	Lower	Benzene is not typically found in food; FDA restricts use in food packaging.
Sediment	Lower	Benzene is a volatile compound that does not undergo significant partitioning or accumulation in sediments.

[1] For more information about child-specific exposure factors, please refer to the Children's Exposure Factors Handbook (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=52047).

[2] The Level of Concern category is a subjective determination by the TEACH Workgroup, U.S. EPA, that reflects potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge.

TOXICITY SUMMARY[3] AND REFERENCE VALUES

Toxicity Summary: Children may be more sensitive than adults to benzene due to exposure and biological susceptibility considerations, but data to adjust for these factors do not currently exist (45). Benzene affects blood-forming (hematopoietic) cells. Epidemiologic and human (adult) case studies show clear evidence of causal association between benzene exposure and certain leukemias (46). The noncancer endpoint (decreased lymphocyte count) used to derive USEPA's RfD and RfC also results from benzene effects on hematopoietic cells (47). Depending on exposure/dose level, one experimental animal study showed persistent damage in blood forming cells (48); other studies showed altered immune function (49, 50); and another study showed skeletal damage, weight retardation, and spontaneous abortion (51).

Carcinogenicity weight-of-evidence classification: U.S. EPA classifies benzene as a known (Category A) human carcinogen under 1986 Risk Assessment Guidelines and as a known human carcinogen for all exposure routes based on convincing human evidence and supporting experimental animal evidence under proposed revised (1996) Carcinogen Risk Assessment Guidelines (http://www.epa.gov/iris/subst/0276.htm, II.A.1).

U.S. EPA RfD for Chronic Oral Exposure: 4E-3 mg/kg/day, based on decreased lymphocyte count in adult humans (http://www.epa.gov/iris/subst/0276.htm, I.A.1). Last revised 4/17/03.

U.S. EPA RfC for Chronic Inhalation Exposure: 3E-2 mg/m^3, based on decreased lymphocyte count in adult humans. (http://www.epa.gov/iris/subst/0276.htm, I.B.1). Last revised 4/17/03.

U.S. EPA Cancer Drinking Water Unit Risk: 4.4E-4 to 1.6E-3 per mg/L. Derived by extrapolation method using linear extrapolation of human adult occupational data (http://www.epa.gov/iris/subst/0276.htm, II.B.1.2). Last revised 11/1/94.

U.S. EPA Drinking Water Concentrations at Specified Risk Levels: 1E-4, 10^2-10^3 µg/L; 1E-5, 10^1-10^2 µg/L; 1E-6, 10^0-10^1 µg/L (http://www.epa.gov/iris/subst/0276.htm, II.B.1). Last revised 11/1/94.

U.S. EPA Drinking Water Advisories (10 kg child): 1 day = 0.2 mg/L; 10 day = 0.2 mg/L. (http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf). Last revised Winter 2004.

[3]The TEACH database focuses on information from studies of immature and/or developing organisms, e.g. mostly *excluding* workplace studies of adults. This toxicity summary is likely to *include* information from workplace or other studies of mature humans or experimental animals if child-specific (i.e. human epidemiology or developmental toxicity) information is lacking for the agent of interest.

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U.S. EPA Inhalation Unit Risk: A range of 2.2E-6 to 7.8E-6 is the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 $\mu g/m^3$ benzene in air. Derived using low-dose linearity extrapolation method utilizing maximum likelihood estimates http://www.epa.gov/iris/subst/0276.htm, II.C.1). Last revised 1/19/00.

U.S. EPA Cancer Oral Slope Factor: 1.5E-2 to 5.5E-2 per (mg/kg)/day, based on increased risk of leukemia in adults http://www.epa.gov/iris/subst/0276.htm II.B.1.1). Last revised 1/19/00.

U.S. EPA MCL (drinking water): 0.005 mg/L, based on anemia, decrease in blood platelets, and increased risk of cancer. (http://www.epa.gov/safewater/mcl.html). Last revised 7/02.

U.S. EPA MCLG: 0. (http://www.epa.gov/safewater/mcl.html). Last revised 7/02.

ATSDR Minimal Risk Level (MRL): 0.05 ppm [0.2 mg/m^3] (acute inhalation; immune system endpoint); 0.004 ppm [0.01 mg/m^3] (intermediate inhalation; neurologic endpoint); no chronic MRL is available. (http://www.atsdr.cdc.gov/mrls.html). Last revised 9/97.

REGULATORY INFORMATION

- Regulatory values for benzene recently revised by the U.S. EPA are Drinking Water Advisories for a 10 kg child, the RfD, and the RfC (see Toxicity section).
- On September 14, 1989 benzene was regulated for certain sources of air pollutant emissions under section 112 of the Clean Air Act (40 CFR Part 61: the "Benzene NESHAP"). Benzene is one of 188 hazardous air pollutants (HAPs) listed under section 112(b) of the 1990 Clean Air Act Amendments and regulated from more than 170 industrial source categories.
- Under the Emergency Planning and Community Right-to-Know Act, the Reportable Quantity for benzene is 10 pounds.

BACKGROUND ON CHEMICAL

CAS Number: 71-43-2

Physicochemical Properties: Go to http://www.ChemFinder.com and search for benzene.

Production: Commercially recovered from coal and petroleum sources and 472 U.S. facilities produce or process 17.2 billion pounds of benzene per year. Benzene ranks in top 20 chemicals for U.S. production volume.

Uses: Benzene is used in the production of solvents, plastics, resins, and some types of rubbers, drugs, and pesticides. Emissions of benzene can be detected from such products as carpet glue, textured carpet, liquid detergent, and furniture wax. Benzene is also a natural part of crude oil, gasoline (1% to 2% benzene), and cigarette smoke.

Environmental Fate: Industrial processes are the main source of benzene in the environment. Benzene can volatilize into the air from water and soil. Benzene can break down within a few days in air, whereas benzene breaks down more slowly in water and soil. It can also leach from the soil into groundwater easily. Benzene does not bioaccumulate in plants or animals.

Synonyms: phenyl hydride; coal naphtha; benzol; cyclohexatriene; benzine; benzolene; phene; 6-annulene; bicarburet of hydrogen; carbon oil; mineral naphtha; motor benzol; nitration benzene; pyrobenzol.

Additional information on benzene is available in the TEACH Scientific Review Table for Benzene, and at the following websites:

www.atsdr.cdc.gov/mrls.html
www.cdc.gov/default.htm
www.epa.gov/epahome/index.html
www.epa.gov/iris/
www.epa.gov/ncea/pdfs/benzenef.pdf
www.epa.gov/tri/
www.epa.gov/ttn/atw/nata/

REFERENCES

1. Axelsson, G., et al. 1984. *British Journal of Industrial Medicine* 41: 305-312.
2. Witkowski, K.M. and N.E. Johnson. 1992. *Social Biology* 39(1-2): 45-54.
3. Chen, D., et al. 2000. *Occupational and Environmental Medicine* 57: 661-667.
4. Wang, X., et al. 2000. *American Journal of Epidemiology* 152(8): 693-700.
5. Buckley, J.D., et al. 1989. *Cancer Research* 49: 4030-4037.
6. McKinney, P.A., et al. 1991. *British Medical Journal* 302: 681-687.
7. Shaw, G., et al. 1984. *American Journal of Epidemiology* 119(5): 788-795.
8. Xiao, O.S., et. al. 1988. *Cancer* 62(3): 635-644.
9. Dowty, B.J., et al. 1976. *Pediatric Research* 10: 696-701.
10. Raaschou-Nielson, O., et. al. 2001. *American Journal of Epidemiology* 153(5): 433-443.
11. Pearson, R. L., et. al. 2000. *Journal of Air and Waste Management Association* (50): 175-180.
12. Reynolds, P., et. al. 2002. *Cancer Causes and Control* 13: 665-673.
13. Amodio-Cocchieri, R., et al. 2001. *Journal of Toxicology and Environmental Health Part A* 63:79-87.
14. Barbieri, A., et al. 2002. *Archives of Environmental Health* 57(3):224-228.
15. Lee, C.R., et al. 2002. *The Science of the Total Environment* 299:237-245.
16. Buchdahl, R. et al. 2000. *Occupational and Environmental Medicine* 57:86-93.
17. Rolle-Kampczyk, U.E., et al. 2002. *Archives of Environmental Health* 57(4):326-331.
18. Sofoluwe, G.O. 1968. *Archives Environmental Health* 16: 670-672.
19. Xing, S.G., et. al. 1992. *Teratogenesis, Carcinogenesis, and Mutagenesis* 12: 223-230.
20. Sharma, R.K., et. al. 1985. *Mutation Research* 158: 217-231.
21. Ciranni, R., et. al. 1988. *Mutation Research* 208: 61-67.
22. Davis, D.L., and A.M. Pope. 1986. *Toxicology and Industrial Health* 2(4): 445-451.
23. Corti, M., and C.A. Snyder. 1996. *Archives of Toxicology* 70: 209-217.
24. Keller, K.A., and C.A. Snyder. 1986. *Toxicology* 42: 171-181.
25. Keller, K.A., and C.A. Snyder. 1988. *Fundamental and Applied Toxicology* 10: 224-232.
26. Hazelton Laboratories America, Inc. 1982. *Inhalation Teratology Study in Rats: Benzene Final Report.* Submitted to American Petroleum Institute, Washington, DC.
27. Ungvary, C. and E. Tatrai. 1985. *Archives of Toxicology* Supplement 8: 425-430.
28. Geist, C.R., et al. 1983. *Perceptual and Motor Skills* 57: 1083-1086.
29. Exxon Biomedical Sciences, Inc. 1986. *Determination of Maternal Toxicity and Fetal Toxicity of Benzene in Rats Following Oral Exposure.* Submitted under the EPA Compliance Audit Program.
30. Bio/dynamics Inc. 1980. *An Inhalation Female Fertility Study with Benzene in Rats*. Project No. 79-2425. Submitted to Chemical Manufacturers Association, Washington, DC.
31. Coate, W.B., et al. 1984. "Inhalation Teratology Study of Benzene in Rats." *In Applied Toxicology of Petroleum Hydrocarbons*. MacFarland, H.N, Holdsworth, C.E., MacGregor, J.A., Call, R.W., and Lane, M.L. (editors). Princeton Scientific Publishers Inc., Princeton, New Jersey. Pages 187-198.
32. Tatrai, E., et. al. 1980. *Journal of Hygiene, Epidemiology and Microbiology and Immunology* 24(3): 363-371.
33. Hudak, A., and G. Ungvary 1978. *Toxicology* 11: 55-63.
34. Brown, J.D., et. al. 1978. *Toxicology and Applied Pharmacology* 46: 9-18.
35. Murray, F.J., et. al. 1979. *American Industrial Hygiene Association Journal* 40(11): 993-998.
36. Ghantous, H., and B.R.G. Danielsson. 1986. *Biological Research in Pregnancy* 7(3): 98-105.

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37. Maltoni, C., et al. 1985. *American Journal of Industrial Medicine* 7: 415-446.
38. Wallace, L.A. 1989. *Cell Biology and Toxicology* 5(3): 297-314.
39. Wallace, L.A., et al. 1985. *Atmospheric Environment* 19(10): 1651-1661.
40. Clayton, C.A., et al. 1999. *Journal of Exposure Analysis and Environmental Epidemiology* 9: 381-392.
41. Pellizzari, E.D., et al. 1999. *Journal of Exposure Analysis and Environmental Epidemiology* 9: 49-55.
42. Wallace, L. 1996. *Environmental Health Perspectives* 104(Suppl. 6):1129-1136.
43. U.S. Environmental Protection Agency, 1991. *Risk Assessment Guidance for Superfund: Volume I-Human Health Evaluation Manual; Part B, Development of Risk-based Preliminary Remediation Goals* (EPA/540/R-92/003) http://www.epa.gov/superfund/programs/risk/ragsb/index.htm
44. U.S. Environmental Protection Agency, 2002. *Draft Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils (Subsurface Vapor Intrusion Guidance)* (OSWER) http://www.epa.gov/epaoswer/hazwaste/ca/eis/vapor.htm
45. U.S. Environmental Protection Agency, IRIS benzene carcinogenicity Support Document, p. 42; http://www.epa.gov/ncea/pdfs/benzenef.pdf
46. U.S. Environmental Protection Agency, IRIS benzene file, http://www.epa.gov/iris/subst/0276.htm, II.A.1.
47. U.S. Environmental Protection Agency, IRIS benzene file, http://www.epa.gov/iris/subst/0276.htm, I.A.1; I.B.1.
48. Keller, K.A., and C.A. Snyder. 1988. *Fundamental and Applied Toxicology* 10: 224-232.
49. Rosenthal, G.J., and C.A. Snyder. 1987. *Toxicology and Applied Pharmacology* 88: 35-43.
50. Rozen, M.G., et. al. 1984. *Toxicology Letters* 20: 343-349.
51. Ungvary, C. and E. Tatrai. 1985. *Archives of Toxicology* Supplement 8: 425-430.